Received: 18 December 2017 | Accepted: 3 January 2018

DOI: 10.1002/clc.22886

PREVENTION WILEY CLINICAL CARDIOLOGY

REVIEW

The connection between the breast and heart in a woman: Breast cancer and cardiovascular disease

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Cardiovascular disease remains the leading cause of death in women in the United States and is a major public health issue for all women, but it is of increasing concern to breast cancer survivors. Advancements in early detection and breast cancer therapy have resulted in over 90% of women surviving 5 years past their diagnosis of breast cancer. Nonetheless, with increased survivorship from breast cancer, there has been an increase in cardiovascular disease in these women. The consequences of the treatments for breast cancer may increase the risk for cardiovascular disease. Additionally, there is an overlap of risk factors common to both breast cancer and cardiovascular disease. The increased risk of cardiovascular disease in women who survive breast cancer must be recognized, with a focus on the prevention and early detection of cardiovascular disease.

KEYWORDS

Acute Coronary Care, Acute Coronary Syndrome, Breast Cancer, Cardiovascular Disease

1 | INTRODUCTION

Cardiovascular disease remains the leading cause of death in women in the United States and is a major public health issue for all women,[1] but it is of increasing concern to breast cancer survivors. Advancements in early detection and breast cancer therapy have resulted in over 90% of women surviving 5 years past their diagnosis of breast cancer, with a related mortality reduction of ~2% per year over the last decade.[2,3] Nonetheless, with increased survivorship from breast cancer there has been an increase in cardiovascular disease in these women.[4] For breast cancer survivors, deaths due to cardiovascular diseases account for 35% of the non–cancer-related deaths in those age 50 years and older, and cardiovascular mortality is the greatest single non–cancer-related cause of death.[5]

Based on the most recent statistics available, 236 968 women were diagnosed with breast cancer in 2014 and 41 211 women died from breast cancer in the United States.[6] The Surveillance, Epidemiology and End Results data and numerous other population studies have demonstrated an increased incidence in cardiovascular disease in breast cancer survivors, compared to other women without breast cancer.[4,5,7]

Although cardiovascular morbidity and mortality is common in breast cancer survivors, earlier research focused primarily on the consequences of treatments for breast cancer as a cause for cardiovascular outcomes. Nonetheless, a recent assessment beyond the effect of cancer therapies has demonstrated an increase in cardiovascular diseases, irrespective of treatment, with an overlap of risk factors common to both diseases. Those individuals with breast cancer have been shown to have a greater prevalence of cardiovascular risk factors.[8] Given that increased cardiovascular risk appears to manifest approximately 5 to 7 years after the initial diagnosis of breast cancer,[4,7] a potential window of opportunity exists for possible preventive intervention strategies, although there are limited intervention trials available to assess effectiveness of specific interventions to date.

2 | CARDIOVASCULAR EFFECTS OF BREAST CANCER THERAPY

There are a number of potential ways that the treatment of breast cancer can result in an increase in cardiovascular disease–specific risk factors or cardiovascular disease. Degree of susceptibility to adverse cardiovascular effects appears to be related to the presence or absence of cardiovascular risk factors or overt cardiovascular disease prior to the onset of breast cancer diagnosis and treatment. This has

been described by Jones et al[9] as a "multiple-hit" hypothesis (Figure 1).

3 | CHEMOTHERAPY AND CARDIOVASCULAR CONSEQUENCES

There is a well-established link between anthracycline therapy and development of congestive heart failure.[10] High cumulative doses of anthracyclines resulted in a risk of heart failure ranging from 3% to 26%.[11] As a result of this knowledge, anthracycline doses have decreased, and the cardiotoxicity effects have been reduced to 2% to 3%.[12] Doxorubicin is the most commonly used chemotherapeutic agent used in breast cancer and is an anthracycline that directly affects cardiovascular function, with the potential to cause type 1 cardiotoxicity, which is irreversible. A more recently developed and very commonly used therapy for breast cancer, trastuzumab, a monoclonal antibody that targets the human epidermal growth factor receptor-2 (HER-2) and other targeted HER-2 therapies, can similarly affect cardiac function. However, trastuzumab may cause type 2 cardiotoxicity, which differs from type 1, in that it is potentially reversible if discovered early. It is estimated that trastuzumab results in a significant reduction of left ventricular (LV) ejection fraction in 7.1% to 18.6% of patients, based on 4 major clinical trials, but clinical heart failure results in only 1.7% to 4.1% of subjects.[13] Outside of clinical trials, the rates of heart failure with trastuzumab use have been much higher, with 1 large registry cohort showing rates of heart failure in 12.1% of those treated with trastuzumab alone, and 20.1% of those treated with trastuzumab in conjunction with an anthracycline.[14] There are great limitations in determining the incidence and prevalence of chemotherapy- and radiotherapy-induced cardiac abnormalities, or chemotherapy-related cardiac dysfunction (CRCD) given differences in definitions, lack of consistent data reporting of consequences of therapies, and selection bias in studies of breast cancer treatment clinical trials. Nonetheless, for

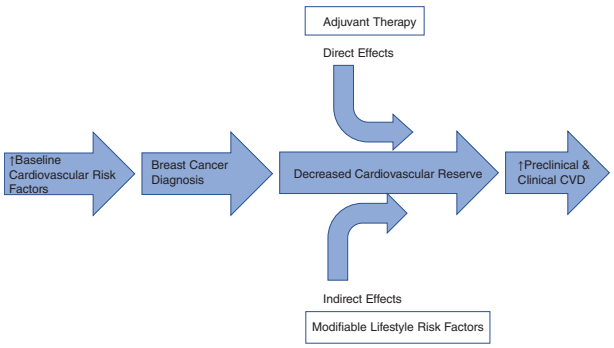

FIGURE 1 A schematic representation describing the "multiple-hit" hypothesis. At diagnosis, a significant proportion of early breast cancer patients present with preexisting or heightened cardiovascular disease (CVD) risk factors, which increase the risk of adjuvant therapy–associated cardiovascular injury. Independently, many adjuvant therapies used in breast cancer are associated with unique and varying degrees of direct adverse effects on the cardiovascular system. These direct effects occur in the context of concomitant lifestyle perturbations (indirect effects) that combine to reduce cardiovascular reserve. Collectively, these changes may leave the patient more susceptible to further cardiovascular insults and at higher risk of premature death due to cardiovascular mortality. From: Jones et al.,[9] with permission

TABLE 1 Risk assessment and monitoring associated with left ventricular dysfunction

Patient-Related Risk Factors	Medication-Related Risk Factors[a]
One point for each risk factor present	High (risk score 4): anthracyclines, trastuzumab, ifosfamide, cyclophosphamide, clofarabine
Age (bimodal distribution): <15 or >65 years	Intermediate (risk score 2): docetaxel, pertuzumab, sunitinib, sorafenib
Female	Low (risk score 1): bevacizumab, imatinib, lapatinib, dasatinib
Hypertension	Rare (risk score 0): etoposide, rituximab, thalidomide
Diabetes mellitus	
Atherosclerosis (coronary artery disease, cerebrovascular disease, peripheral artery disease)	
Preexisting heart disease or heart failure	
Prior anthracycline	
Prior radiation therapy to the chest	
Cardiotoxicity risk score	
Medication-related risk score + number of patient-related risk factors = CRS >6: very high; CRS 5–6: high; CRS 3–4: intermediate; CRS 1–2: low; CRS 0: very low	
Mayo Clinic monitoring recommendations	
Very high risk: echocardiogram with GLS before every (other) cycle, end, 3–6 months, and 1 year; optional ECG, cTn with echocardiogram during chemotherapy	
High risk: echocardiogram with GLS every 3 cycles, end, 3–6 months, and 1 year after treatment; optional ECG, cTn with echocardiogram during chemotherapy	
Intermediate risk: echocardiogram with GLS, midterm, end, and 3–6 months after treatment; optional ECG, cTn midterm of chemotherapy	
Low risk: Optional echocardiogram with GLS and/or ECG; cTn at the end of treatment	
Very low risk: None	

Abbreviations: cTn, serum cardiac troponin. ECG, electrocardiogram; GLS, global longitudinal strain.
Risk assessment, cardiotoxicity risk score at the time of baseline assessment and monitoring for patients undergoing anticancer therapy. From: Herrmann et al.,[38] with permission.
[a] Medication-related risk factor (1–4) was based on the risk for a decline or dysfunction in the ventricular function.

patients who undergo a myocardial biopsy to determine the cause of cardiac dysfunction, those with chemotherapy-induced cardiomyopathy have the poorest prognosis of all cardiomyopathies.[15] Different models to predict the risk of heart failure prior to initiation of trastuzumab have been proposed with age, sex, anthracycline use, known coronary artery disease, atrial fibrillation, renal failure, and cardiovascular risk factors appearing to affect the risk of heart failure development.[16,17]

4 | RADIATION THERAPY AND CARDIOVASCULAR CONSEQUENCES

Radiation to the breast may have direct effects to the myocardium, but the data are conflicting regarding the association of breast radiation and accelerated atherosclerosis. It is estimated that the heart receives 1 to 5 Gy of radiation when undergoing radiation therapy for breast cancer. In a case control study from Sweden and Denmark of women with breast cancer who underwent radiation therapy from 1958 to 2001, the rates of major coronary events were linearly associated with the mean radiation dose to the heart, where for every 1 Gy of radiation, the risk for coronary events increased by 7.4% ($P < 0.001$).[18] The increased risk started within the first 5 years after radiation therapy, and those with more cardiovascular risk factors had an increased risk of cardiovascular events, but the proportional increase of cardiovascular events by radiation dosage was the same. Older studies have shown an increased risk of cardiac morbidity and mortality with radiation, particularly left-sided breast cancer, but this was observed with higher doses of radiation than are used in our current era.[19] More recent studies have had conflicting results, with many single institution studies and large data registries showing no increased cardiovascular risk,[20–22] whereas others support an increased risk for cardiovascular disease associated with radiation.[23,24] Nonetheless, a recent meta-analysis spanning the years 2010 to 2015 demonstrated a mean radiation dose to the heart of 4.4 Gy and a hazard ratio for cardiovascular deaths of 1.30 ($P < 0.001$) for those who received radiation compared with those who did not, with a proportional increase in cardiac mortality of 0.04 per Gy.[25]

5 | SHARED RISK FACTORS FOR BREAST CANCER AND CARDIOVASCULAR DISEASE

There is significant overlap in risk factors for cardiovascular disease and breast cancer (Figure 2). This overlap of risk factors for 2 very different diseases is often overlooked, and should be a consideration for the treatment provider when addressing future health risks beyond the necessary treatment for breast cancer. The recognition of this overlap may help women breast cancer survivors address modifiable risk factors for heart disease after breast cancer treatments are completed.

Breast cancer and cardiovascular disease are associated with strong evidence supporting inflammation as a mediator of both disease processes.[26,27] Chronic inflammation is associated with oxidative stress, and this too is associated with both disease processes, so it is not surprising that certain diseases and exposures that increase inflammation and oxidative stress may be risk factors for both diseases. Tobacco use and poor diet affect the risk of both diseases.[28] There is significant epidemiological data showing that increased physical activity is associated with a reduced risk for both cardiovascular disease and cancer.[29] Diabetes is a significant risk factor for cardiovascular disease, but its impact on breast cancer is also established. Insulin resistance, as seen in type 2 diabetes mellitus, promotes estrogen and testosterone release in women, and these sex steroids may be causal in the relationship between diabetes and breast cancer.[30] There is evidence linking breast cancer in postmenopausal women with obesity, making obesity another risk factor for both diseases.[31] Hyperlipidemia, particularly elevated levels of low-density lipoprotein (LDL), is a well-established risk factor for atherosclerosis, whereas it has been suggested that elevated LDL may be associated with the development of breast cancer (in contrast with all other cancers).[32] A well-established nonmodifiable risk factor for breast cancer is both the *BRCA1* and *BRCA2* gene mutation. Interestingly, these BRCA

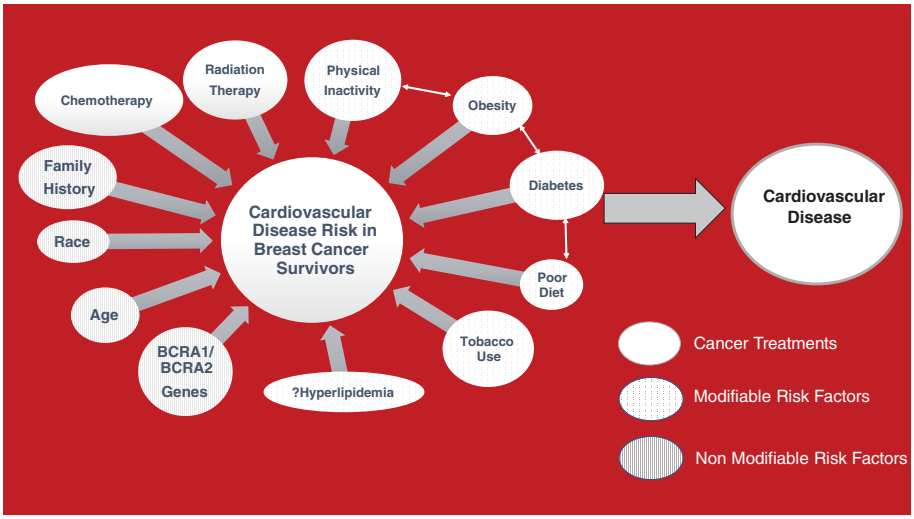

FIGURE 2 The impact of cancer treatment and cardiovascular risk factors on breast cancer survivors impacting the development of heart disease. Cancer treatment that can impact cardiovascular risk depicted in white. Nonmodifiable cardiovascular risk factors depicted by lines. Modifiable cardiovascular risk factors depicted by dots

genes are also involved in preservation of cardiac function, and abnormalities may affect susceptibility to cardiac damage. It has been observed that the presence of either of these gene abnormalities is associated with a higher risk of heart failure in patients receiving anthracycline-based therapies, irrespective of duration and dosing of anthracycline exposure.[33,34]

Breast cancer survivorship has been increasing and comprises the largest group of cancer survivors in the United States.[35] Despite the increased risk of cardiovascular disease in breast cancer survivors, there are no specific guidelines for the assessment and prevention of cardiovascular risk in these patients. In fact, the current American survivorship guidelines endorsed by all major cancer societies do not recommend any specific cardiovascular screening beyond the usual cardiovascular risk monitoring for the general population.[36] Recently, recommendations for preferential echocardiographic baseline and surveillance imaging of breast cancer patients before and during therapy have evolved to improve early detection of CRCD.[37]

6 | CARDIOVASCULAR DISEASE PREVENTION IN BREAST CANCER SURVIVORS: RECOMMENDATIONS

6.1 | Risk Assessment and Monitoring

Over the last decade, guidelines for risk assessment and monitoring of breast cancer patients have been evolving. Before the initiation of breast cancer therapy, it is recommended that patients undergo a thorough history and physical examination to determine baseline cardiovascular risk and potential for cardiac toxicity. A cardiovascular risk assessment tool has been developed (Table 1), which provides a scoring system and approaches to proactive management for risk mitigation.[38] Baseline assessment and surveillance cardiac monitoring during cancer therapy has been recommended in women undergoing breast cancer treatment. Initial monitoring protocols were based on biomarker (troponin) and radionuclide angiographic LV function assessments. An increase in cardiac troponin[39] or decrease in left ventricular ejection fraction (LVEF)[40] has been shown to be associated with clinical heart failure. More recently, echocardiography has emerged to be a preferential imaging modality in breast cancer patients, not only because this technique can assess LVEF without radiation exposure, a particular concern in women with breast cancer, but moreover, the highly sensitive echocardiographic strain modality can detect reductions in subclinical LV systolic function before a reduction in LVEF is observed.[41,42] Echocardiographic strain is a measure of regional myocardial deformation obtained by angle-independent 2-dimensional (2D) speckle tracking, and is a standard feature now provided by vendors of all commercially available cardiac ultrasound machines. Thus, it is currently recommended that all women undergoing breast cancer treatment have baseline 2D echocardiography with strain imaging, with follow-up routine surveillance imaging during therapy, at intervals determined by the specific cancer therapeutic regimen.[37,43] If a reduction in strain or LVEF is noted, appropriate interventions with cardioprotective medications (β-blockers and/or angiotensin-converting enzyme inhibitors) and/or adjustments to cancer treatment schedule can be implemented. Multidisciplinary patient-centric cardio-oncology teams have evolved to provide optimal management of breast cancer patients, and include oncologists, radiotherapists, and cardiologists. Although trastuzumab and related agents have no late cardiac toxicities, this is not true for anthracyclines. At the current time, the precise interval for long-term imaging follow-up of breast cancer survivors has not been determined. Clinical practice suggests follow-up at 6 months and 1 year of cancer therapy completion, and then at least at 5-year intervals, in asymptomatic patients who have received anthracycline therapies, but this may need to be adjusted according to individual prognosis, cardiovascular risks, and comorbidity profile.

7 | CONCLUSION

Breast treatment has evolved rapidly, resulting in over 90% survival, making breast cancer survivors the largest cancer survivorship group in the United States. As a result of common risk factors, the effects of chemotherapy and radiation, and shared genetic and environmental impact on both diseases, a greater risk of cardiovascular disease in these women is observed when compared to the general population. The traditional atherosclerotic cardiovascular disease risk assessment does not account for this increased risk. Additionally, the oncology guidelines to date for survivors of breast cancer do not recommend additional cardiovascular surveillance. It is paramount that we begin to recognize this increased risk of cardiovascular disease in women who survive breast cancer, and focus our work on the prevention of cardiovascular disease and its early detection.

Conflicts of interest

The authors declare no potential conflicts of interest.

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How to cite this article: Gulati M, Mulvagh SL. The connection between the breast and heart in a woman: Breast cancer and cardiovascular disease. *Clin Cardiol*. 2018;41:253–257. https://doi.org/10.1002/clc.22886